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SOCIETY FOR WOMEN'S HEALTH RESEARCH

PRESENT

THE STATE OF THE ART IN THE MANAGEMENT OF

Inflammatory Bowel Disease

IN COOPERATION WITH:

Crohn's & Colitis Foundation of America

The American College of Gastroenterology

American Gastroenterological Association

North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

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THE STATE OF THE ART IN THE MANAGEMENT OF INFLAMMATORY BOWEL DISEASE

INTRODUCTION

Inflammatory bowel disease (IBD) traditionally comprises two principal categories: ulcerative colitis (UC) and Crohn's disease (CD). Together, the two conditions afflict approximately one million Americans, producing a range of symptoms that include persistent diarrhea, rectal bleeding, abdominal pain, weight loss, and delayed growth and sexual maturation in children.[1] Patients with IBD are at increased risk for osteoporosis, colon cancer, primary sclerosing cholangitis, pyoderma gangrenosum, and other extraintestinal complications. The destructive impact of these symptoms on patients' well-being, quality of life, and capacity to function is often profound. Because IBD is a chronic condition that usually has a peak onset before the age of 30 years, its management generally requires lifelong monitoring and intervention.

Although surgery may become necessary to treat complications or refractory disease, pharmacotherapy remains the cornerstone of management. The precise pathogenesis of IBD is not known, but it is believed to result from chronic upregulation of the immune system in the intestinal mucosa.[2] Thus, pharmacotherapy for IBD is geared toward addressing this immunopathology.

A broad and expanding range of options is available for this purpose. Aminosalicylates and antibiotics remain the first line of therapy in mild to moderate UC and CD. Corticosteroids, immunomodulators, and biologic therapies are available for patients with more severe disease.

The wide array of options available for managing IBD makes it possible for the clinician to tailor the treatment approach to the individual patient's needs and preferences. Treatment individualization is essential to ongoing adherence, which in turn enhances the likelihood of a favorable long-term clinical outcome. Among the considerations to be taken into account in designing a regimen for either form of IBD are the extent and severity of disease, the presence of complications, the patient's response to current and prior treatments, and the current therapeutic objective (that is, whether the aim is to induce remission or to maintain it).

Sex differences are another consideration that needs to be taken into account in the design of a treatment regimen for IBD. Sex differences in IBD are an important issue, but it is an area in which, unfortunately, our knowledge base is far from complete. There are some things we do know in this regard, however, and this information should be considered in devising treatment plans. We know, for example, that whereas IBD affects men and women equally, CD is 20% more common in females and UC is 20% more common in males.[3] It is also known that certain comorbid conditions—specifically, depression and irritable bowel syndrome—are more common in females than in males, and another common comorbidity, endometriosis, affects exclusively women. In addition, sex may have important effects on selection of surgical procedures, since, as we will see later, some procedures are more likely than others to offer the opportunity to preserve fertility in female patients. We also know that gender plays a significant role in patients' adherence to their therapeutic regimen. Much less is known, however, about the effect of sex differences in connection with pharmacotherapy for IBD. Sex differences have historically been underresearched, primarily because, until recently, women were often not included in clinical trials. The rationale given for their exclusion was that it was for the protection of possibly pregnant women; in addition, it was believed that women's hormonal cycling might somehow skew trial results.[4] This situation is beginning to change, however, and a recently published study from the Food and Drug Administration (FDA) reported that in recent years, women have been participating in clinical trials at nearly the same rate as men.[5] The evaluation of sex differences in efficacy, safety, and pharmacokinetic parameters of drugs used to treat IBD should be a focus of future investigations.

LEARNING OBJECTIVES

After completing this program, participants will be able to discuss what is known about, to summarize current findings, and to identify knowledge gaps as they apply to the:

- Clinical utility of traditional and evolving medical treatments in inducing remission in ulcerative colitis and Crohn's disease
- Clinical utility of traditional and evolving medical treatments in maintaining remission in ulcerative colitis and Crohn's disease
- Use of surgical procedures in the management of inflammatory bowel disease
- Relationship between adherence and disease relapse to optimize adherence in clinical practice

Target audience: US and Canadian gastroenterologists and fellows

MEDICAL TREATMENT OF UC

UC is characterized by mucosal inflammation limited to the colon; there is rare "backwash ileitis." It almost always involves the rectum, and it

TABLE 1

AGENTS FOR INDUCING REMISSION IN UC

Mild Disease	Moderate Disease	Severe Disease
■ 5-ASAs or sulfasalazine • Topical (distal disease) • Oral (extensive disease) • Combination	■ 5-ASAs or sulfasalazine • Topical (distal disease) • Oral (distal disease) ■ Corticosteroids • Topical (distal disease) • Oral (distal/extensive disease)	■ IV corticosteroids ■ IV cyclosporine

UC=ulcerative colitis; 5-ASA=5-aminosalicylic acid; IV=intravenous.

Adapted with permission from Stein RB, et al. *Gastroenterol Clin North Am.* 1999;28:297-321.

The State of the Art in the Management of Inflammatory Bowel Disease, as published in this *Clinical Courier*®, is the first of a series of newsletters based, in part, on the proceedings of a conference that was held on December 12-13, 2001, in Washington, DC. Learning objectives of that conference were as follows:

By the end of the program, participants were able to discuss what is known about sex differences and were able to summarize current findings and identify knowledge gaps as they apply to the:

- Epidemiology and proposed etiologies of ulcerative colitis and Crohn's disease
- Clinical and diagnostic findings in adults and children with IBD
- Clinical utility of traditional and evolving therapies in the everyday management of ulcerative colitis and Crohn's disease
- Psychosocial challenges IBD patients face
- Relationship between adherence and disease relapse to optimize adherence in clinical practice

Statement of Need: Strategies for the management of IBD are continuing to evolve as the result of research advances, growing clinical experience, and an expanding therapeutic armamentarium. This progress is paving the way toward more efficient approaches to the differential diagnosis of IBD as well as more effective methods of establishing and maintaining remission. Unique treatment considerations in special populations such as women, children and adolescents, and the elderly are also gaining greater recognition. An appreciation of these ongoing developments is crucial to optimizing therapeutic responses, reducing the risk of complications, and improving the quality of life for the approximately one million Americans who suffer from IBD. Awareness of these issues will help physicians become better equipped to meet the challenges of IBD in daily clinical practice and will support the practice of evidence-based medicine.

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may extend in a circumferential and uninterrupted pattern to involve part or all of the colon.[6] Bloody diarrhea, rectal urgency, and tenesmus are the cardinal symptoms of UC. Its most dangerous acute complications are toxic colitis and perforation, and its most lethal long-term complication is colon cancer.

Inducing Remission in Patients With UC

The anatomic extent and clinical severity of the disease are key determinants of treatment selection (Table 1).[2] Disease extent is classified as either distal or extensive; distal UC is characterized by inflammation that is limited to the area below the splenic flexure, whereas extensive UC is characterized by inflammation that extends proximal to the splenic flexure. Disease severity can be classified as mild (less than four stools per day, with or without blood, and no systemic signs of toxicity), moderate (more than four stools per day with minimal signs of toxicity), or severe (more than six bloody stools per day, accompanied by signs of toxicity, including fever, tachycardia, anemia, or elevated erythrocyte sedimentation rate).[6] However, symptoms most typically occur along a spectrum of severity, and many patients will fall somewhere in the middle of these classifications. Remission in UC is defined by the ability of the colonic mucosa to regenerate and heal with resolution of inflammatory symptoms.

For mild to moderate disease, the 5-aminosalicylic acid (5-ASA) agents are the treatment of choice; they are generally administered orally for extensive disease and orally and/or rectally for distal disease (Table 2).[2] Sulfasalazine, which consists of sulfapyridine bound to 5-ASA, was the first of the agents in this category to be developed, as well as the first major therapeutic advance in the treatment of UC.[7] A major drawback to its use, however, is the fact that doses that would provide optimal efficacy also tend to be associated with unacceptable side effects; approximately 15% to 30% of patients treated with the agent develop adverse effects, such as nausea, vomiting, dyspepsia, anorexia, and headache. Less common but more serious adverse effects include bone marrow suppression, connective tissue disorders, hemolytic anemia, megaloblastic anemia, and sperm abnormalities.[6,7] Pancreatitis, hepatotoxicity, allergic reactions, and nephrotoxicity are infrequent side effects of all of the 5-ASA agents.

The development of sulfa-free 5-ASA preparations has enabled the administration of higher doses of mesalamine, the pharmacologically active

TABLE 2

ORAL 5-ASA PREPARATIONS

Generic Name (Trade Name)	Constituents	Site of Delivery
Sulfasalazine (Azulfidine®)	Sulfapyridine + 5-ASA	Colon only
Mesalamine		
(Asacol®)	5-ASA	Distal ileum, colon
(Pentasa®)	5-ASA	Proximal jejunum to colon
(Claversal®, Salofalk®)	5-ASA	Ileum, colon
Balsalazide disodium (Colazal™)	5-ASA + 4-aminobenzoyl-β-alanine	Colon only
Olsalazine sodium (Dipentum®)	5-ASA dimer	Colon only

Adapted with permission from Stein RB, et al. *Gastroenterol Clin North Am*. 1999;28:297-321.

ingredient of sulfasalazine, while substantially diminishing adverse effects and systemic toxicity.[2] In equimolar doses, the oral mesalamine preparations are equivalent in efficacy to sulfasalazine; however, there is limited systemic absorption resulting in side effects as mentioned previously.[7] Overall, their safety profile is similar to that of placebo, even at high doses.[8] Up to 75% of patients with mild to moderate UC will improve on 2 g/day of 5-ASA, and the dose-response continues up to at least 4.8 g/day.[2,9] Adequate dosing is crucial throughout the continuum of treatment, including induction as well as maintenance therapy. In addition, the same dose that induced symptom remission should be continued to maintain it.[2] Although a proportion of sulfasalazine-intolerant patients will be intolerant to mesalamine as well, intolerance is not typical, and an estimated 80% to 90% of sulfasalazine-intolerant patients will tolerate mesalamine without difficulty.[6]

For mild to moderate distal disease, rectally administered mesalamine (enemas or suppositories) or corticosteroids (foams or enemas) may be used alone or in combination with oral aminosalicylates for more distal disease. A recent meta-analysis of 67 trials in patients with distal UC demonstrated that mesalamine enemas were 10% to 20% more effective than either oral mesalamine alone or most corticosteroid enemas.[10] Combination oral and topical therapy may yield even greater results. Doses of 2.4 g/day of oral mesalamine combined with a once-nightly mesalamine rectal enema have been shown to cease rectal bleeding in more patients and more quickly (vs oral, *P*=.002; vs rectal, *P*=.04) than either therapy alone.[11] Physicians must be careful to develop an effective therapeutic regimen for these patients, who may find ongoing use of enemas or suppositories objectionable and decide to discontinue treatment.

Oral corticosteroids have long been used in the treatment of UC, but they are best reserved for moderate to severe disease or for cases that are refractory to optimal doses of aminosalicylates.[2,6] The rationale for limiting their use is their well-known propensity to cause intolerable and potentially serious adverse effects, including hyperglycemia, fluid retention, fat redistribution, cataracts, osteonecrosis, osteoporosis, myopathy, and psychiatric disorders.[2] Corticosteroids are associated with a dose-response effect, but greater efficacy is attained at the expense of a proportionate increase in adverse effects.[6] It is generally recommended that oral prednisone be administered at a dosage of 40 to 60 mg/day until remission is achieved and that the dosage then be tapered in increments of 5 to 10 mg/week until a dosage of 20 mg/day is reached; thereafter, a taper rate of 2.5 mg/week is suggested.[6]

For patients with severe-fulminant UC, intravenous (IV) corticosteroids or IV cyclosporine can be considered.[2] Azathioprine or 6-mercaptopurine (6-MP) is indicated as a maintenance agent for refractory UC or for corticosteroid-dependent patients and after inductive therapy with cyclosporine.[12]

Maintaining Remission in Patients With UC

Remission in UC is characterized not only by the absence of inflammatory symptoms, including diarrhea, bleeding, and urgency, but also by regeneration of intact mucosa, with no ulceration, granularity, or friability. To maintain remission once it is established, the vast majority of patients will require ongoing maintenance therapy; lifelong pharmacotherapeutic maintenance is generally recommended.[6]

The approach to maintenance is dictated by the approach that was taken to induction. When remission has been attained with aminosalicylates,

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OFF-LABEL USAGE

Generic Name	Trade Name	Approved Use (if any)	Unapproved/ Investigational Use
Azathioprine (derivative of 6-mercaptopurine)	Imuran®	Rheumatoid arthritis and renal transplantation	Crohn's disease and ulcerative colitis
Budesonide	Pulmicort Turbuhaler®; Rhinocort®; Entocort™	Asthma and allergic rhinitis Crohn's disease	N/A
CDP-571 (anti-TNF-α monoclonal antibody)	N/A	N/A	Crohn's disease and ulcerative colitis
Ciprofloxacin	Cipro®	Various aerobic bacterial infections	Crohn's disease
Cyclosporine	Sandimmune®; Neoral®	Allogeneic transplantation, rheumatoid arthritis, and psoriasis	Crohn's disease and ulcerative colitis
5-Aminosalicylate mesalamine olsalazine sodium balsalazide disodium	Asacol®; Pentasa®; Rowasa®; Canasa® Dipentum® Colazal™	Ulcerative colitis	Crohn's disease
Glucocorticoids (hydrocortisone, prednisone, and prednisolone)	Various	Ulcerative colitis and numerous other indications	N/A
Infliximab (anti-TNF-α monoclonal antibody)	Remicade®	Moderately to severely active Crohn's disease refractory to conventional treatments, fistulizing Crohn's disease, and rheumatoid arthritis	Ulcerative colitis and other inflammatory disorders
Methotrexate	Various	Neoplastic disease, psoriasis, and rheumatoid arthritis	Crohn's disease
6-Mercaptopurine	Purinethol®	Chemotherapy, leukemia, and transplantation	Crohn's disease and ulcerative colitis
Metronidazole	Flagyl®	Trichomoniasis *(Trichomonas vaginalis)*, amebiasis, and anaerobic bacterial infections	Crohn's disease
Sulfasalazine	Azulfidine®	Ulcerative colitis	Crohn's disease
Tacrolimus (FK506)	Prograf® Protopic®	Allogeneic transplantation Atopic dermatitis	Primary sclerosing cholangitis, Crohn's disease, and ulcerative colitis

TNF=tumor necrosis factor; N/A=not available

whether oral or rectal, these agents can be continued. As is the case with induction, the efficacy of these agents for maintenance is dose dependent. Although sulfasalazine 4 g/day is effective in preventing relapse, a substantial proportion of patients will suffer considerable side effects at this dosage. Mesalamine is also associated with dose-dependent increases in efficacy, and dosages up to 4.8 g/day have been shown to have no increase in adverse effects[6]; therefore, it is often recommended that the dosage used to establish remission be continued for purposes of maintaining it.[2] This approach minimizes risk of relapse due to premature reduction of dose and has been demonstrated to be effective in up to 75% of patients.[2] A meta-analysis of 11 trials involving 1153 patients demonstrated that the other oral formulations of mesalamine are as effective as sulfasalazine for maintenance therapy.[7]

Corticosteroids have been shown to have no benefit when used as maintenance therapy.[2] Therefore, aminosalicylates are often used as maintenance therapy after corticosteroids have been tapered. However, azathioprine or 6-MP may be necessary for some patients who require corticosteroids to induce remission in order to reduce the corticosteroid dose subsequently; these agents can also be used to maintain remission induced by cyclosporine.

Patients with left-sided disease who require topical 5-ASA therapy to attain remission may need continuing topical therapy to sustain it. Mesalamine in enema or slow-release suppository form has been shown to maintain remission for up to 1 year in dosages as low as 1 g/day.[13,14] Although enema administration every other day or three times weekly may be effective for some patients, efficacy is likely to be greater with daily administration and may be effective for re-establishing remission in patients who relapse on less frequent dosing.[10,14] Dosing frequency is more important than the size of the dose in these patients. As with all 5-ASA treatments, topical mesalamine should be continued at the same dose once remission is established to prevent relapse.

The combination of oral and topical mesalamine may be particularly effective for maintaining remission. In a 1-year double-blind study of 72 patients who had experienced two or more relapses in the previous year but were currently in remission, relapse occurred in only 36% of patients randomized to combined therapy (oral mesalamine 1.6 g/day plus topical mesalamine 4 g/100 mL twice weekly) compared with 64% of patients who received oral therapy alone.[15]

Treating Patients With Refractory UC

Refractory UC is characterized by continuing severe symptoms despite optimal doses of oral aminosalicylates (4 to 6 g/day of sulfasalazine or 4.8 g/day of mesalamine), oral corticosteroids (40 to 60 mg/day of prednisone), and topical medications.[6] Refractory disease may be the result of inadequate dose or delivery of aminosalicylates, intercurrent infections, concurrent use of nonsteroidal anti-inflammatory agents, concomitant irritable bowel syndrome, aminosalicylate intolerance, or treatment nonadherence.

The recommended therapy for refractory disease is IV corticosteroids at a daily dose equivalent to 300 mg of hydrocortisone or 48 mg of methylprednisolone for patients who have received corticosteroids in the preceding month, or possibly IV adrenocorticotropic hormone for patients who have not received corticosteroids in the preceding month. Higher doses of corticosteroids have not proven to be beneficial.[6] In rare cases, resumption of cigarette smoking or the addition of antibiotics or infliximab may be effective in treating refractory disease. Nicotine therapy, IV cyclosporine, and the addition of probiotics have been used as "alternative" approaches. Colectomy is indicated when these efforts fail, when intolerable adverse effects develop as a result of medical treatment, or in the presence of dysplasia or cancer.

MEDICAL TREATMENT OF CD

CD is a chronic transmural inflammation that may affect any part of the alimentary tract from mouth to anus. On initial presentation, nearly 40% of all cases involve both the small and the large bowel (ileocolitis), usually contiguously. About a third of cases are confined to the small bowel (regional enteritis), usually involving the terminal ileum (ileitis), and approximately 25% of cases are confined to the colon alone.[16] Perianal lesions occur in approximately 15% to 20% of patients, but they are rarely the sole presenting site of CD.[17] Although they are rarely clinically important, oral and gastroduodenal lesions will often be found on careful observation.

CD usually presents with local signs and symptoms of intestinal inflammation, but the condition tends to evolve into a clinical pattern that is defined by either stricturing (obstructive) or penetration (fistulizing). Since CD usually produces inflammation in the ileocecal region, the most common early symptoms are abdominal pain in the lower right quadrant, tenderness, and diarrhea, frequently with low-grade fever, anorexia, and weight loss. Localized microperforations in the ileocecal area may produce acute right lower quadrant signs and symptoms, mimicking appendicitis, whereas microperforations in the sigmoid area may produce left lower quadrant manifestations, mimicking diverticulitis.

Obstructive symptoms are among the most common as CD proceeds, since the transmural inflammation of the condition produces fibromuscular proliferation in the intestinal wall, followed by luminal narrowing. Alternatively, as inflammation burrows through the entire thickness of the bowel wall, sinus tracts are formed; these tracts often penetrate the serosal surface and fistulize into adjacent tissues and even through the skin. Perianal fistulae and other lesions of the perineum are among the most distressing and mutilating complications, but they do not necessarily parallel the activity or severity of the intestinal disease.

Inducing Remission in Patients With CD

The choice of a medication for inducing remission in CD depends on the location of the disease, its severity, and the patient's experience with previous therapies. Location is a consideration because certain agents are not effective in some areas; for example, corticosteroids are not effective in perianal CD. Severity is a consideration because it determines the balance of efficacy and toxicity. For example, an agent that is somewhat less effective but has a low risk of toxicity may be appropriate for a patient with mild symptoms, whereas the price of greater toxicity may be worth paying for greater effectiveness in the patient with more severe symptoms. Finally, the patient's past experience is an important guide to treatment choice; if a patient has suffered intolerable side effects as a result of taking a particular medication, alternate types of agents should be considered when selecting a new regimen.

Several options are available for inducing remission in CD (Table 3). A primary objective in the management of CD is to establish remission

TABLE 3

AGENTS FOR INDUCING REMISSION IN PATIENTS WITH CD

Mild to Moderate CD*	Moderate to Severe CD	Severe CD
• Sulfasalazine	• Prednisone	• Hospitalization
• Mesalamine	• Budesonide	• IV corticosteroids
• Metronidazole	• Azathioprine	• Infliximab
• Ciprofloxacin	• 6-MP	• IV antibiotics
	• Methotrexate	• IV cyclosporine/ oral tacrolimus
	• Infliximab	• Surgery
	• IV antibiotics	• Total parenteral nutrition

CD=Crohn's disease; 6-MP=6-mercaptopurine

*Majority of patients.

From Hanauer SB, et al. *Am J Gastroenterol*. 1997;92:559-566.

without using corticosteroids whenever possible, since these agents may elicit intolerable side effects even at low doses and cause corticosteroid dependency within 1 year in more than a third of patients.[18] Treatment should be targeted toward the site of disease, taking into consideration the specific release profiles of the available agents. Optimal dosages should be used to maximize the likelihood of a complete response (Table 4).[2]

TABLE 4

THERAPEUTIC DOSAGES FOR INDUCING REMISSION IN PATIENTS WITH CD

Agent	Dosage
Sulfasalazine	3-6 g/day
Mesalamine (5-ASA)	1.5-4.0 g/day (with increased efficacy at 4.0-g dose)
Corticosteroids	0.25-0.75 mg/kg/day for IV methylprednisolone 40-60 mg/day for PO prednisone
Azathioprine	2-3 mg/kg/day
6-MP	1.5 mg/kg/day
Metronidazole	10-20 mg/kg/day
Methotrexate	15 mg/week for PO or 25 mg/week IM or SC
Cyclosporine	5.0-7.5 mg/kg/day PO in chronically active CD; 4 mg/kg/day IV in severe CD and refractory fistulae*
Infliximab	Single 5-mg/kg infusion

PO=oral; IM=intramuscular; SC=subcutaneous.

*Uncontrolled trials.

Adapted with permission from Stein RB, et al. *Gastroenterol Clin North Am.* 1999;28:297-321.

The 5-ASA compounds are safe and effective for establishing remission in mild to moderate CD. The efficacy of sulfasalazine is dose related, but so are the adverse effects, which are related to the sulfapyridine moiety. The efficacy of mesalamine also increases over the dosage range up to 4 g/day, but because the compound lacks the sulfapyridine moiety, adverse effects do not increase with increasing dose. A landmark placebo-controlled trial conducted by Singleton and colleagues was the first to demonstrate the benefit of mesalamine; in this study, after 16 weeks of treatment, 43% of patients who had received mesalamine 4 g/day had attained remission, compared with 18% of patients who had received placebo ($P \leq .0017$). Efficacy was clearly dose related, with 23%, 24%, and 43% of patients responding to daily doses of 1 g, 2 g, and 4 g, respectively.[19] Unfortunately, subsequent trials with mesalamine have failed to distinguish a therapeutic effect that is superior to placebo. Additional trials are under way to evaluate the further efficacy of even higher doses of mesalamine (6 g/day) for induction of remission. Mesalamine is currently considered first-line therapy for mild to moderate Crohn's disease.[20]

Corticosteroids are effective in inducing remission in CD; however, these agents are typically reserved for moderate to severe disease and are rarely used as monotherapy because of the substantial toxicity associated with their use. Corticosteroids are generally used as an add-on agent to aminosalicylates. When this approach is taken, treatment should be initiated with a dose sufficient to induce remission, and an effort should be made to wean the patient off the corticosteroid as quickly as possible. Budesonide, a newer agent in the corticosteroid class, has fewer short-term corticosteroid-related adverse effects and was recently approved by the FDA for inducing remission in mild to moderate CD involving the ileocecal area. In one 8-week double-blind trial, budesonide 9 or 15 mg/day brought about remission in 51% and 43% of patients, respectively, compared with 20% for placebo.[21] The agent, however, has been demonstrated to be ineffective as maintenance therapy.[22] Questions still remain regarding the long-term safety of budesonide as pertains to bone loss and cataract formation.

The immunomodulators azathioprine and 6-MP have shown promise in establishing remission in CD. A meta-analysis of randomized, placebo-controlled trials including a total of 367 patients found an odds ratio for response of 3.09 (95% confidence interval [CI], 2.45 to 3.91), with an odds ratio for a corticosteroid-sparing effect of 3.69 (95% CI, 2.12 to 6.42).[23] In one analysis of 6-MP in 276 patients with CD and 120 with UC, 7.6% experienced toxic effects directly attributable to the drug, including pancreatitis, bone marrow suppression, drug-induced hepatitis, and infections.[24] The laboratory measurement of 6-MP metabolites has become a valuable tool for monitoring toxicity.

Azathioprine and 6-MP can be given in combination with the 5-ASAs, but it is important to note that drug interactions that can rarely lead to bone marrow suppression occur between these agents.[25] As long as white blood cell counts are monitored, however, this interaction can be turned to therapeutic advantage, since concomitant 5-ASA therapy allows the use of lower doses of azathioprine or 6-MP, resulting in lower costs and possibly a more rapid response.[26]

Methotrexate is effective for establishing remission when administered intramuscularly at a dosage of 25 mg/week. The agent has been found to be associated with substantial activity at approximately 6 weeks and to provide a corticosteroid-sparing effect. Adverse effects occur fairly frequently, however, with the most common being nausea and vomiting, cold symptoms, abdominal pain, joint pain, and fatigue.[27] In addition, routine evaluation of blood counts and liver enzymes is necessary because of the agent's potential toxicities, which include myelosuppression and hepatotoxicity.[2] In general, 6-MP should be tried before methotrexate except in patients who cannot tolerate or have failed to respond to the former agent.

High-dose IV cyclosporine or oral tacrolimus (a newer agent currently under investigation for the indication to induce remission in CD) may be considered for patients with severe disease who do not respond to other agents but are poor surgical candidates. IV cyclosporine at a dosage of 4 mg/kg/day has been shown to bring about a response in 80% or more of patients with refractory fistulae within a mean of 7.4 days.[28] However,

the agent has the potential for substantial and wide-ranging toxicities and adverse effects, including hypertension, nephrotoxicity, encephalopathy, pulmonary toxicity, nausea and vomiting, paresthesias, tremors, electrolyte imbalance, and myelosuppression. Patients may also be at an increased risk of convulsions, particularly those patients who are using cyclosporine in combination with high-dose methylprednisolone.[29] Therefore, administration should be limited to experienced centers where blood levels can be monitored.[2]

In the setting of fistulous disease, infliximab has been found to be quite effective, particularly at a dosage of a single infusion of 5 mg/kg. This approach may be useful for patients who have not responded to 5-ASAs, corticosteroids, or other immunomodulators. In a study in which 108 treatment-refractory patients were randomized to receive various doses of infliximab or placebo, 81% of patients responded to the 5-mg/kg dose, whereas 50% responded to the 10-mg/kg dose and 64% responded to the 20-mg/kg dose; the overall response rate was 65% for active treatment, compared with 17% for placebo (P<.001).[20] The agent has also been shown to be associated with a significant increase in the proportion of patients attaining at least a 50% reduction in draining fistulae (P=.002).[30] Infliximab is not without risk, however, and many questions about its use remain unanswered. As of June 2001, 84 cases of tuberculosis have been reported in connection with infliximab, and invasive fungal and other opportunistic infections have been reported as well.[31] The FDA has since received additional reports for a total of 117 cases of infliximab-associated tuberculosis as of November 30, 2001.[32] In addition, infliximab should not be administered in patients with congestive heart failure, as it has been found to worsen this condition.[33] Along with other anti–tumor necrosis factor-α therapies, infliximab has been implicated as a risk factor in demyelinating central nervous system lesions and should be avoided in patients with multiple sclerosis.[34]

Maintaining Remission in Patients With CD

The goals of maintenance therapy are to prolong periods of remission (by downregulating the overactive immune system, suppressing aggressive immunologic factors, and suppressing inflammation), reduce the risk of cancer, and improve quality of life. Regardless of the regimen chosen for maintenance, the clinician should ensure that the patient is receiving an adequate dose (Table 5),[35] as underdosing is a primary reason for relapse. Although the 5-ASAs are clearly effective in inducing remission in CD, their role in maintaining remission is less supported by data from clinical trials. A meta-analysis of 15 randomized, controlled trials involving a total of 2097 patients demonstrated that mesalamine significantly reduced the risk of relapse following surgically induced, but not medically induced, remission (P=.0028).[36] However, a more recent study in 318 patients, not included in the meta-analysis, failed to confirm this postsurgical benefit.[37] In the aggregate, however, the bulk of the evidence appears to favor 5-ASA therapy. Once again, adequate dosing is crucial, and nothing is risked by raising the dose, since the efficacy of mesalamine is dose related, but its adverse effects are not. Optimal results are achieved when the maintenance dose equals the induction dose.

TABLE 5

THERAPEUTIC DOSAGES FOR MAINTAINING REMISSION IN PATIENTS WITH CD

Agent	Dosage
Mesalamine	≥3 g/day
Corticosteroids	Not indicated
Azathioprine	2.5 mg/kg/day
6-MP	1.5 mg/kg/day
Methotrexate	15-25 mg/week (IM or SC)

Hanauer SB, et al. *Am J Gastroenterol.* 1999;92:559-566.

Azathioprine and 6-MP are generally effective in the maintenance of remission in patients who have achieved remission with corticosteroids, but the duration of therapy has yet to be defined. Delayed leukopenia is a risk with this approach, so periodic laboratory monitoring is a necessity.[35] Corticosteroids are ineffective as maintenance therapy for CD.[35]

EVOLVING AND FUTURE TREATMENTS FOR IBD

An extremely broad range of treatments—including agents targeted against TNF, leukocyte adhesion, T_H1 polarization, and T-cell depletion, and other miscellaneous therapies—are in various stages of investigation for the treatment of IBD (Table 6). The agents that appear to have shown the greatest promise thus far in the treatment of CD include tacrolimus, CDP571, and natalizumab. Although it is not yet clear which of these treatments now being investigated will survive the investigational stage into clinical use and which responses will be seen among different patient populations, it seems certain that biologics and other emerging therapies will play an important role in the future treatment of IBD.

TABLE 6

EVOLVING AND FUTURE THERAPIES FOR IBD

Anti-TNF Therapies
- CDP571
- Etanercept
- Soluble p55 receptor (onercept)
- CNI-1493 (MAP kinase inhibitor)
- Thalidomide

Anti–Leukocyte Adhesion Therapies
- Anti-α4 integrin (natalizumab)
- Anti-α4β7 (LDP-02)
- Antisense to ICAM-1 (Isis 2302)

Inhibitors of T_H1 Polarization
- Anti-interleukin 12
- Anti-interferon-γ
- Interleukin 10
- Anti–interleukin-2 receptor (daclizumab, basiliximab)

Anti-CD4
- cM-T412
- MAX
- 16H5
- BF-5

Growth Factors
- Epidermal growth factor
- Keratinocyte growth factor-1 (KGF-1)
- KGF-2 (repifermin, a homolog of KGF-1)

Miscellaneous
- Interferon-β
- G-CSF (filograstim)
- GM-CSF (sargramostim)
- Growth hormone (somatotropin)
- Interleukin 11
- Tacrolimus
- 6-Thioguanine
- Nicotine and nicotine agonists
- Probiotic bacteria (VSL#3, *Escherichia coli* Nissle 1917)
- Medroxyprogesterone acetate

IBD=inflammatory bowel disease; TNF=tumor necrosis factor; MAP=mitogen-activated protein; ICAM=intracellular adhesion molecule; G-CSF=granulocyte colony-stimulating factor; GM-CSF=granulocyte-macrophage colony-stimulating factor.

SURGICAL OPTIONS IN THE TREATMENT OF IBD

Ulcerative Colitis

Surgery is curative for UC, and approximately 30% of patients with the condition will require it at some point in their lives.[38] Urgent indica-

tions for surgery include fulminant toxicity and perforation/bleeding, whereas elective indications include intractability, growth retardation, corticosteroid dependency, medication side effects, cancer/dysplasia, and extraintestinal disease.

A number of surgical techniques are possible. Restorative proctocolectomy has replaced proctocolectomy and ileostomy as the "gold standard" procedure for surgical cure of UC. Most pouch constructions are of the J variety, with S pouches being reserved for patients for whom anatomic reach of the pouch to the anus poses problems; stapled operations are perhaps the most frequent method of anastomosis of the pouch to the anal canal, providing early continence superior to that obtained with the hand-sewn technique. The primary early complications include sepsis and fistula, whereas bowel obstruction and pouchitis are the primary late complications. The procedure can be carried out in one or two stages, but the two-stage approach has the advantages of safety and shorter length of hospital stay. Among several recent advances in this area are techniques to salvage the pelvic pouch when complications occur and the use of probiotics, which hold promise for the prevention and treatment of some cases of pouchitis.

Three additional techniques are available for use in the treatment of UC. Subtotal colectomy/ileostomy is a staging operation used for patients with toxicity, megacolon, perforation, and hemorrhage. Total colectomy/ileorectal anastomosis, now rarely performed, may be considered for patients with minimal rectal involvement, for young female patients to help maintain tube patency and fertility, and for patients with metastatic cancer complicating UC. Finally, continent ileostomy is a complex operation involving the creation of an ileal reservoir from the terminal 60 cm of intestine; indications include a patient's wish to convert from a Brooke ileostomy, salvage of a failed ileoanal operation, and poor sphincter function.

Crohn's Disease

The small intestine is regarded as a nonrenewable resource, so efforts are generally made to avoid or postpone surgical intervention as long as possible in patients with CD. Nevertheless, most of these patients will require surgery at least once, and many will need it several times. Clinicians generally agree on two key principles: resection of diseased intestinal segments is preferred over bypass procedures and bowel, especially small bowel, conservation is highly desirable.

Intestinal obstruction and septic complications, such as internal fistulae or abscess, constitute the primary indications for surgery in CD; others include failure of medical therapy, hemorrhage, growth retardation (in the pediatric population), perforation, and carcinoma. Surgical alternatives for colonic CD include subtotal/total colectomy with or without anastomosis for patients with rectal sparing and toxicity/sepsis, respectively. For patients with pancolitis, proctocolectomy and ileostomy are performed in one or two stages. Many groups follow the policy outlined in Table 7 for treating these patients.

TABLE 7

SUGGESTED APPROACHES TO SURGICAL TREATMENT OF PATIENTS WITH CD

Condition	Suggested Approach
Acute bowel obstruction	Treat medically
Chronic, recurrent obstruction	Resection or strictureplasty
Duodenal obstruction	Strictureplasty or bypass procedure
Abdominal abscess	Drain (if possible), then elective resection
Symptomatic fistulae	Resection bowel
Nonobstructed, nonperforated segment	Treat medically

IBD MANAGEMENT ADHERENCE CHALLENGES

UC and CD require lifelong management, and adherence to prescribed treatment regimens is crucial if patients are to maximize their prospects for favorable outcomes. Although clinicians often assume that their patients take their medication as prescribed, the fact is that patients with IBD often take their medication when they are ill but discontinue when the disease is quiescent, and adherence often decreases dramatically after 1 or 2 years.[39] This trend is most regrettable, given that ongoing adherence to prescribed therapies has been shown not only to be a significant contributor to relapse in quiescent disease,[40] but also to provide a protective effect against colon cancer.[41] Nonadherence may take any of several forms, including failure to fill a prescription, consumption of too much or too little medication, alteration of dosing regimens, or incorrect self-administration (particularly with enema therapy).[39]

Factors affecting adherence can be categorized as relating to the illness, to the patient, or to the treatment.[39] With regard to the illness, patients who have well-controlled IBD with few flares are most likely to discontinue maintenance therapy. Patient-related factors include degree of education received from healthcare providers, comprehension of instructions for proper medication use, understanding of the consequences of nonadherence, extent of self-management skills and abilities, and availability of a support system.[39] Sex is another important patient-related factor that impacts adherence; in a study of 94 patients with quiescent UC being treated with mesalamine, nonadherence was found to be significantly less common in women ($P<.05$).[42] The reasons for this sex difference is not clear; however, it has been shown that although men and women with IBD share some concerns, women have greater concerns than do men about feelings related to their bodies, attractiveness, feeling alone, and having children.[43]

Treatment-related factors that affect adherence include efficacy, safety and tolerability, convenience (including frequency of dosing and number of pills), formulation (including mode of delivery and pill size), and cost (which may prevent patients from being able to purchase medication).[39] Although all of these issues are important, tolerability may be particularly so, and clinicians should ask patients which side effects they would find difficult or impossible to live with and make an effort to prescribe a well-tolerated regimen. Among the 5-ASA compounds, sulfasalazine is associated with a variety of dose-related effects (including nausea, dyspepsia, fever, headaches, and sperm abnormalities) due to intolerance of the sulfa moiety.[6,7] Immunomodulators are associated with side effects that include fever and rash, nausea, pancreatitis, and leukopenia.

As previously noted, however, mesalamine lacks the sulfa moiety, and although its efficacy is dose related, its adverse effects are not; therefore, doses can be increased to optimal levels with minimal risk of intolerability.[8] Since convenience of administration contributes to adherence as well, it is important to note that a recent study of dosing frequency demonstrated that delayed-release mesalamine concentrations are the same regardless of whether the agent is administered in three divided doses or in a single daily dose.[44]

Another way to promote adherence to pharmacotherapy is to emphasize to patients the benefits that will accrue as a result. Pharmacotherapy for IBD not only enables patients to feel and function better by controlling symptoms, but there is also growing, though preliminary, evidence that it may also reduce colorectal cancer risk—something that greatly concerns most patients. In a retrospective study conducted by Moody and colleagues, patients adherent to sulfasalazine for more than 4 months had a 3% risk of developing colorectal cancer, whereas those who were nonadherent had a 31% risk ($P<.001$).[45] Furthermore, in a study conducted by Eaden and colleagues, patients who took mesalamine at a dosage of at least 1.2 g/day for a period of years reduced their cancer risk by 91% (odds ratio, 0.09, 95% CI, 0.03 to 0.28; $P<.00001$).[46]

The keys to optimizing adherence are individualization (based on the patient's disease and treatment histories, responses to previous medications, "track record" of taking treatments as prescribed, and cost considerations), education of the patient and family, and a productive physician-patient interaction that fosters open communication. Treatment of IBD is most likely to be successful when the clinician employs the full range of treatment options in a manner that respects the patient's unique needs and desires.[39]

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1. Which portion of sulfasalazine is responsible for the agent's dose-related adverse effects?
   a. The salazine moiety
   b. The sulfa moiety
   c. The pyridine moiety
   d. None of the above

2. Which of the following is the treatment of choice for mild to moderate UC?
   a. 5-ASAs
   b. Methotrexate
   c. Corticosteroids
   d. Azathioprine

3. When the 5-ASA agents are used to induce remission in UC or CD, how should the dose of these agents be titrated for maintenance therapy?
   a. The dose for maintenance should be 15% lower than the dose used to induce remission.
   b. The dose for maintenance should be 25% lower than the dose used to induce remission.
   c. The 5-ASA agents should not be used for maintenance therapy.
   d. The dose for maintenance should be the same as the dose used to induce remission.

4. Which of the following agents offers no benefit when used for maintenance of remission in UC?
   a. Aminosalicylates
   b. Corticosteroids
   c. Azathioprine
   d. 6-MP

5. When 6-MP or azathioprine is given in combination with the 5-ASAs, which step usually needs to be taken with regard to dosing?
   a. The dose of 6-MP or azathioprine needs to be decreased.
   b. The dose of 6-MP or azathioprine needs to be increased.
   c. The dose of the 5-ASA needs to be decreased.
   d. The agents are contraindicated in combination.

6. Which of the following is a potential culprit in refractory UC?
   a. Inadequate dose or delivery of aminosalicylates
   b. Intercurrent infections
   c. Treatment nonadherence
   d. Concurrent use of nonsteroidal anti-inflammatory agents
   e. All of the above

7. In which abdominal region does early CD most frequently produce pain?
   a. The upper left quadrant
   b. The lower left quadrant
   c. The upper right quadrant
   d. The lower right quadrant

8. Which dose of IV corticosteroids is currently recommended for treatment of refractory UC?
   a. The equivalent of 100 mg/day of hydrocortisone
   b. The equivalent of 250 mg/day of hydrocortisone
   c. The equivalent of 300 mg/day of hydrocortisone
   d. IV corticosteroids are not recommended for the treatment of refractory UC

9. Which procedure is currently considered the surgical treatment of choice for UC?
   a. Restorative proctocolectomy
   b. Proctocolectomy and ileostomy
   c. Subtotal colectomy/ileostomy
   d. Total colectomy with ileorectal anastomosis

10. Who are more likely to be nonadherent?
    a. Men
    b. Women

Please record your posttest answers:

1. ____ 2. ____ 3. ____ 4. ____ 5. ____ 6. ____ 7. ____ 8. ____ 9. ____ 10. ____

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   ❑ Yes ❑ No
   Please be as specific as possible: _____

4. Do you believe the newsletter contained pharmaceutical industry bias?
   ❑ Yes ❑ No
   Comments: _____

5. How do you prefer to receive continuing medical education information?
   (On a scale of 5 to 1, please score each of the following:
   5 = very useful; 3 = somewhat useful; 1 = don't use)
   _____ a. Newsletter
   _____ b. Video
   _____ c. Audiotape
   _____ d. Monograph/Journal Supplement
   _____ e. Symposium/Conference
   _____ f. CD-ROM/Computer Based

6. Do you believe such materials, sponsored by educational grants from industry, are:
   _____ 10 very appropriate/useful, 0 not appropriate/useful?

7. Actual amount of time I spent in this activity: _____ hours(s)

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Specialty _____

Address _____

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